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Acute kidney injury after lung cancer surgery
Incidence and clinical relevance, predictors, and role of N-terminal pro B-type natriuretic peptide

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A B S T R A C T

Background: Acute kidney injury (AKI) frequently occurs in several medical and surgical settings, and it is associated with increased morbidity and mortality. In patients undergoing lung cancer surgery, AKI has not been fully investigated. We prospectively evaluated the incidence, clinical relevance, and risk factors of AKI in patients undergoing lung cancer surgery. Moreover, we estimated the accuracy of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the prediction of AKI.
Methods: Patients undergoing lung cancer surgery were included in the study. Plasma NT-proBNP was measured before and soon after surgery. Postoperative AKI was defined according to the Acute Kidney Injury Network (AKIN) classification.
Results: A total of 2179 patients were enrolled. Of them, 222 (10%) developed AKI and had a more complicated in-hospital clinical course (overall complication rate: 35% vs. 16%; $P < 0.0001$), and a longer hospital stay (10 ± 7 vs. 7 ± 4 days; $P < 0.0001$). The incidence of AKI increased in parallel with the extent of lung resection. Among the independent predictors of AKI, serum creatinine (area under the curve [AUC] 0.70 [95% CI 0.67-0.74]) and NT-proBNP (AUC 0.71 [95% CI 0.67-0.74]) provided the highest predictive accuracy, and their combination further significantly improved AKI prediction (AUC 0.74 [95% CI 0.71-0.77]). No difference in AKI prediction was observed between preoperative and postoperative NT-proBNP ($P = 0.84$).
Conclusions: Acute kidney injury occurs in 10% of patients undergoing lung cancer surgery, and it is associated with a high incidence of postoperative complications. The risk of AKI can be accurately predicted by the combined evaluation of preoperative serum creatinine and NT-proBNP.

1. Introduction

Acute kidney injury (AKI) is a frequent complication occurring in a variety of clinical settings, particularly in critically ill patients and after major surgical procedures [1,2]. In particular, its incidence ranges from 5% after general surgery to over 30% after cardiac surgery [3–7]. The development of AKI, as well as its severity, is independently associated with an increase in morbidity and mortality, length of hospital stay, and costs [1,4–7]. Efforts to change the clinical course of AKI have substantially failed because therapeutic measures are currently lacking, early detection is challenging when serum creatinine (sCr) or urine output changes are used to identify AKI, and accurate clinical predictors are not well known [1,2].

In patients undergoing lung cancer surgery, the issue of postoperative AKI, in terms of incidence, clinical relevance, and identification of risk predictors, has not been fully addressed. Acute kidney

Abbreviations: AKI, acute kidney injury; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sCr, serum creatinine; eGFR, glomerular filtration rate was estimated; RRT, renal replacement therapy

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injury has been reported to occur in 3%–9% of patients undergoing thoracic surgery for lung cancer [8–10]; however, these figures may not reflect the current true incidence due to the retrospective study design, inconsistent definition criteria, and nonsystematic measurements of sCr levels.

Recent attention has been focused on natriuretic peptides as potential predictors of postoperative events after cardiac and non-cardiac surgery, including cardiovascular complications, prolonged length of hospital stay, and short-term and long-term mortality [11–13]. Levels of B-type natriuretic peptide (BNP) and of its precursor, N-terminal pro-B-type natriuretic peptide (NT-proBNP) have also been found to accurately predict AKI in both surgical and medical clinical settings [14–20]. However, due to the paucity of research in this area, the possible association between natriuretic peptides and AKI after lung cancer surgery still remains to be elucidated.

The purpose of this prospective study was to determine the incidence, the predictors, and the clinical relevance of AKI development in an unselected population of consecutive patients undergoing lung cancer surgery. Moreover, we investigated the accuracy of NT-proBNP, measured before and soon after surgery, in the prediction of AKI.

2. Material and methods

2.1. Study population

This prospective, observational study was conducted at the European Institute of Oncology between February 1 st, 2010 and October 31 st, 2016. We enrolled all consecutive patients undergoing elective thoracic surgery for lung cancer. Patients in chronic peritoneal or hemodialysis treatment, with evidence of AKI before surgery, exposed to contrast agents in the previous seven days, and those without at least one daily sCr sample for two consecutive days after surgery were excluded. The study was approved by the Institutional Review Board (S365/407), and written informed consent was obtained from all patients.

2.2. Study protocol

Clinical evaluation, electrocardiogram, chest x-ray, and pulmonary function tests were part of the preoperative assessment. Plasma NT-proBNP concentration was measured at baseline (before surgery) and soon after surgery (within 1 h).

Serum creatinine was measured at baseline (before surgery) and once a day for the first 2 days aftes surgery, using the Jaffe method. Glomerular filtration rate was estimated (eGFR) by using the simplified Modification of Diet in Renal Disease (MDRD) formula [21]. Postoperative AKI was defined applying the Acute Kidney Injury Network (AKIN) classification according to the maximal increase in sCr within the first 48 h after thoracic surgery from baseline: Stage 1 was defined as a $\geq$ 0.3 mg/dl sCr increase; Stage 2 as a > 2- to 3-fold sCr increase; Stage 3 as a > 3-fold sCr increase or sCr $\geq$ 4.0 mg/dl with an acute increase > 0.5 mg/dl, or need for renal replacement therapy (RRT), irrespective of the stage at the time of RRT [22].

The surgical variables recorded included surgical procedure, thoracotomy or thoracoscopy approach, duration of surgery, intraoperative fluid balance, and blood loss. Thoracoscopy cases converted to open thoracotomy were recorded as open cases.

In addition to AKI, in-hospital death, as well as major clinical complications (bleeding, acute respiratory failure, pneumonia, sepsis, need for surgical revision, acute coronary syndromes, arrhythmias, heart failure, stroke, and thromboembolism), and length of stay were collected.

2.3. NT-proBNP measurements

For determination of the serum NT-proBNP levels, blood samples were centrifuged at 1000 x g for 10 min and stored at −30 °C until analysis. NT-proBNP was measured using a radial partition immunoassay (Stratus CS – Siemens Healthcare Diagnostic, Deerfield, Illinois). We used different cut-off levels according to gender and age: 63.9 ng/L for men and 125 ng/L for women aged ≤49 years, 125 ng/L for men and 186 ng/L for women aged from 50 to 59 years, and 194 ng/L and 204 ng/L for men and women aged ≥60 years.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation, and they were compared using *t*-test for independent samples. Variables not normally distributed are presented as median and interquartile ranges, and they were compared with the Wilcoxon rank sum test. Categorical data were compared using $\chi 2$ test or Fisher exact test, as appropriate. Spearman correlation was used to detect the possible relationship between the sCr value at admission and the extent of its increase after surgery (maximum value - admission value).

A multivariable logistic model was developed to identify the independent predictors of AKI with stepwise selection of variables, and results are presented as odds ratios (OR) with 95% confidence intervals (CI). The initial set of potential predictors undergoing selection included those variables **showing a univariate** association with AKI (P value < 0.10). Receiver Operating Characteristic (ROC) curves were calculated, and the area under the ROC curve (AUC) with 95% CI was used to measure the ability of each independent AKI predictor. AUCs were compared as recommended by DeLong et al. [23]. As baseline sCr and NT-proBNP showed the highest AKI predictive accuracy, net reclassification improvement (NRI) was used to identify their possible additional role. The reported NT-proBNP values were adjusted for age and gender. Moreover, we explored the complementary predictive value for AKI (OR and 95% CI) of baseline sCr (< or > median value of the study patients) and of preoperative NT-proBNP (high or normal value) considered together in the entire population.

All tests were 2-tailed, and P < 0.05 was required for statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Reclassification statistics were assessed with the SAS macros published by Cook and Ridker [24].

3. Results

A total of 2179 patients undergoing lung cancer surgery (1331 men; age 63 ± 10 years) were enrolled in this study. Of these patients, 222 (10%) developed AKI: Stage 1 AKI occurred in 200 (90%) patients, Stage 2 in 15 (7%), and Stage 3 in 7 (3%) patients. Five (2%; 0.2% of the entire population) AKI patients required RRT. When the RIFLE (Risk, Injury, Failure, Loss, and End-Stage Renal Failure) threshold for sCr increase was used (sCr × 1.5 versus admission) [25], AKI occurred in 5% of the study patients.

The baseline clinical characteristics, intraoperative variables, and postoperative complications of patients with and without AKI are shown in Table 1. Patients with AKI were older and more likely to be male and to have hypertension and a lower eGFR. Preoperative and postoperative NT-proBNP levels were significantly higher in patients who developed AKI than in those without AKI. Moreover, they experienced a greater intraoperative blood loss. As expected, patients with AKI had a more complicated clinical course and a longer hospital stay. The incidence of AKI increased in parallel with the extent of lung resection (Fig. 1).

The independent preoperative and intraoperative predictors of AKI found at multivariable analysis are reported in Table 2. Among them, baseline sCr and NT-proBNP provided the highest predictive accuracy at ROC analysis, with no significant difference between the two curves (P = 0.88; Fig. A1). However, the combination of baseline sCr and NT-proBNP significantly improved AKI prediction accuracy when compared to the AUC of each of the two variables (P < 0.01 for both